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=> d his

     (FILE 'HOME' ENTERED AT 10:53:33 ON 21 MAR 2002)

     FILE 'HCAPLUS' ENTERED AT 10:53:51 ON 21 MAR 2002
L1        563519 S N OR NEISSERIA
L2          2532 S L1 (2W) (MENINGITIDI?)
L3             5 S NHHA OR NHHA/AB OR HIA HOMOLOG OR (HIA HOMOLOG)/AB
L4             2 S NH HA OR (NH HA)/AB OR N HHA OR ( N HHA)/AB
L5             7 S L3 OR L4
L6             2 S L5 AND L1
L7          3858 S NEISSERI?/AB
L8             0 S L4 AND L7
L9             2 S L5 AND L7
L10            2 S L9 OR L6
L11           21 S L2 (L) SURFACE (L) ANTIGEN#
L12            1 S L5 AND ANTIGEN#

     FILE 'HCAPLUS' ENTERED AT 10:58:21 ON 21 MAR 2002
L13            4 S L11 (L) (DELET? OR MUTAT? OR MODIF? OR TRUNCA? OR FRAGM?)
L14            5 S L10 OR L12 OR L13

=> d .ca l14 1-5

L14  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:565074  HCAPLUS
DOCUMENT NUMBER:          135:151626
TITLE:                    Proteins comprising conserved regions of
                          Neisseria meningitidis surface antigen
                          NhhA
INVENTOR(S):              Peak, Ian Richard Anselm; Jennings, Michael Paul
PATENT ASSIGNEE(S):       University of Queensland, Australia
SOURCE:                   PCT Int. Appl., 91 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2001055182      A1   20010802      WO 2001-AU69     20010125
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2000-177917P  P  20000125
AB   Novel proteins that constitute modified forms of a Neisseria
     meningitidis surface antigen and encoding nucleic acids are provided.  The
     modified surface proteins are characterized by having deletions of
     non-conserved amino acids, and thereby being capable of eliciting
     cross-protective immune responses against Neisseria
     meningitidis.  The invention extends to the use of the modified surface
     antigens in diagnostics, in therapeutic and prophylactic vaccines and in
     the design and/or screening of medicaments.  The modified surface antigens
```

are particularly useful in vaccines which effectively immunize against a broader spectrum of N. meningitidis strains than would be expected from a corresponding wild-type surface antigen.

IC ICM C07K014-22
ICS C12N015-31

CC 15-2 (Immunochemistry)
Section cross-reference(s): 1, 3

ST **Neisseria** meningitidis surface **antigen NhhA** vaccine

IT **Mutation**
(**deletion**; proteins comprising conserved regions of **Neisseria meningitidis surface antigen NhhA** for use in diagnostics, therapeutics and prophylactic vaccines)

IT Gene, microbial
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**nhhA**; for surface **antigens** of **Neisseria** meningitidis)

IT DNA sequences
Drug design
Drug screening
Molecular cloning
Neisseria meningitidis
Protein sequences
Vaccines
(proteins comprising conserved regions of **Neisseria** meningitidis surface **antigen NhhA** for use in diagnostics, therapeutics and prophylactic vaccines)

IT Nucleic acids
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(proteins comprising conserved regions of **Neisseria** meningitidis surface **antigen NhhA** for use in diagnostics, therapeutics and prophylactic vaccines)

IT **Antigens**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surface, **NhhA**; proteins comprising conserved regions of **Neisseria** meningitidis surface **antigen NhhA** for use in diagnostics, therapeutics and prophylactic vaccines)

IT 227940-22-9 227941-11-9 227941-22-2 227941-24-4 227941-26-6
227941-28-8 227941-30-2 262997-71-7 352405-24-4 352405-25-5
352405-26-6 352405-27-7 352405-28-8 352405-29-9 352405-30-2
352405-31-3 352405-32-4 352405-33-5 352405-34-6 352405-35-7
352405-36-8 352405-37-9 352405-38-0
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; constructs of **Neisseria** meningitidis surface **antigen NhhA** for use in diagnostics, therapeutics, and prophylactic vaccines)

IT 352405-39-1 352405-40-4 352405-41-5 352405-42-6 352405-43-7
352405-44-8 352405-45-9 352405-46-0 352405-47-1 352405-48-2
352405-49-3 352405-50-6 352405-51-7 352405-52-8 352405-53-9
352405-54-0
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU

(Occurrence); USES (Uses)
(nucleotide sequence; constructs of **Neisseria** meningitidis surface **antigen NhhA** for use in diagnostics, therapeutics, and prophylactic vaccines)

IT 352406-00-9, 1: PN: WO0155182 SEQID: 40 unclaimed DNA 352406-01-0
352406-02-1 352406-03-2 352406-04-3 352406-05-4 352406-06-5
352406-07-6 352406-08-7, 9: PN: WO0155182 SEQID: 48 unclaimed DNA
352406-09-8 352406-10-1 352406-11-2
RL: PRP (Properties)
(unclaimed nucleotide sequence; proteins comprising conserved regions of **Neisseria** meningitidis surface **antigen NhhA**)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:101286 HCAPLUS
DOCUMENT NUMBER: 134:161879
TITLE: Novel strategy for carbohydrate-based therapeutic vaccines
INVENTOR(S): Jennings, Harold J.; Sad, Subash; Guo, Zhongnu; Liu, Tianmin; Yang, Qinling
PATENT ASSIGNEE(S): National Research Council of Canada, Can.
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001009298	A2	20010208	WO 2000-CA886	20000728

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: CA 1999-2279134 A 19990729

AB The sialic acid component of a sialic acid unit-contg. cell surface marker characteristic of cancerous mammalian cells, such as <a2-8 polysialic acid, is modified, so that cells normally expressing such a marker express instead a modified sialic acid unit-contg. cell surface marker which is strongly immunogenic. For example, the present invention enables, in a portion of patient cells which regularly express .alpha.2-8 polysialic acid (i.e. various types of cancer cells), the expression of a highly immunogenic surface antigen namely, modified .alpha.2-8 polysialic acid. The modification is suitably N-acylation of a precursor of the sialic acid, so that the N-acylated precursor becomes chem. incorporated in the polysialic acid during its intracellular biochem. synthesis. Antibodies specific for the modified antigen, which can be induced using a conjugate of a suitable portion of the modified sialic acid unit-contg. marker (such as .alpha.2-8 polysialic acid) and a protein, can then be used to eliminate cells which express <a2-8 polysialic acid. Vaccines can be prepd. utilizing conjugates of the modified sialic acid-contg. marker, or utilizing antibodies produced in response to exposure of a suitable

subject to the modified sialic acid-contg. marker, for managing cancer conditions which involve cancer cells characterized, at least in part, by expression of modified sialic acid unit contg. marker.
IC ICM C12N015-00
CC 15-2 (Immunochemistry)
IT **Neisseria meningitidis**
(group B, polysaccharide; conjugates of **modified** .alpha.2-8 polysialic acid and **surface antigen** as therapeutic vaccines)

L14 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:469888 HCAPLUS
DOCUMENT NUMBER: 133:234834
TITLE: Identification and characterization of a novel conserved outer membrane protein from **Neisseria** meningitidis
AUTHOR(S): Peak, I. R. A.; Srikhanta, Y.; Dieckelmann, , M.; Moxon, E. R.; Jennings, M. P.
CORPORATE SOURCE: Department of Microbiology and Parasitology, The University of Queensland, Brisbane, 4072, Australia
SOURCE: FEMS Immunol. Med. Microbiol. (2000), 28(4), 329-334
CODEN: FIMIEV; ISSN: 0928-8244
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A homolog of the adhesin AIDA-I of Escherichia coli was identified in N. meningitidis. This gene was designated **nhhA** (**Neisseria hia homolog**), as anal. of the complete coding sequence revealed that it is more closely related to the adhesins Hia and Hsf of Haemophilus influenzae. The sequence of **nhhA** was detd. from 10 strains and found to be highly conserved. Studies of the localization by Western immunoblot anal. of total cell proteins and outer membrane complex prepns. and by immunogold electron microscopy revealed that **NhhA** is located in the outer membrane. A strain survey showed that **nhhA** is present in 85/85 strains of N. meningitidis representative of all the major disease-assocd. serogroups, based on Southern blot anal. It is expressed in the majority of strains tested by Western immunoblot.
CC 10-1 (Microbial, Algal, and Fungal Biochemistry)
ST gene outer membrane protein **Neisseria**
IT Proteins, specific or class
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(OMP (outer membrane protein); novel conserved outer membrane protein from **Neisseria** meningitidis)
IT Gene, microbial
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(**nhhA**; novel conserved outer membrane protein from **Neisseria** meningitidis)
IT **Neisseria** meningitidis
(novel conserved outer membrane protein from **Neisseria** meningitidis)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:344861 HCAPLUS
DOCUMENT NUMBER: 131:4240
TITLE: Immunoglobulin molecules having a synthetic variable region and modified specificity

INVENTOR(S): Burch, Ronald M.
PATENT ASSIGNEE(S): Euro-Celtique, S.A., Bermuda
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925378	A1	19990527	WO 1998-US24302	19981113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 9925379	A1	19990527	WO 1998-US24303	19981113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9914597	A1	19990607	AU 1999-14597	19981113
AU 9914598	A1	19990607	AU 1999-14598	19981113
AU 737457	B2	20010823		
EP 1030684	A1	20000830	EP 1998-958584	19981113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1032420	A1	20000906	EP 1998-958583	19981113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001526021	T2	20011218	JP 2000-520811	19981113
BR 9815289	A	20011226	BR 1998-15289	19981113
BR 9815580	A	20020129	BR 1998-15580	19981113
JP 2002507544	T2	20020312	JP 2000-520812	19981113
US 2002028469	A1	20020307	US 2001-963232	20010926

PRIORITY APPLN. INFO.:

US 1997-65716P	P	19971114
US 1998-81403P	P	19980410
US 1998-191780	A1	19981113
WO 1998-US24302	W	19981113
WO 1998-US24303	W	19981113

AB The invention provides modified Ig mols., particularly antibodies, that immunospecifically bind a first member of a binding pair which binding pair consists of the first member and a second member, which Igs have a variable domain contg. one or more complimentary detg. regions that contain the amino acid sequence of a binding site for the second member of the binding pair. The first member is a tumor antigen or an antigen of an infectious disease agent, and the second member is a mol. on the surface of an immune cell. The invention further provides for therapeutic and diagnostic use of the modified Ig.

IC ICM A61K039-395
ICS C12N005-12; C12N015-13; C07K016-42; C07K016-08; C07K016-30
CC 15-3 (Immunochemistry)

Section cross-reference(s): 3

IT **Neisseria meningitidis**
(opa receptor; **modified** Ig mols. having a synthetic variable region and **modified** specificity for tumor **antigen** or **antigen** of infectious agent and **surface** mol. of immune cell)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:451090 HCAPLUS
DOCUMENT NUMBER: 121:51090
TITLE: Microevolution with a clonal population of pathogenic bacteria: recombination, gene duplication and horizontal genetic exchange in the opa gene family of Neisseria meningitidis
AUTHOR(S): Hobbs, Marcia M.; Seiler, Andrea; Achtman, Mark; Cannon, Janne G.
CORPORATE SOURCE: Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27599, USA
SOURCE: Mol. Microbiol. (1994), 12(2), 171-80
CODEN: MOMIEE; ISSN: 0950-382X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Opacity (Opa) proteins are a family of antigenically variable outer-membrane proteins of Neisseria meningitidis. Even among clonally related epidemic meningococcal isolates, there is greater variation of Opa protein expression than can be accounted for by the opa gene repertoire of any individual strain. The authors characterized the opa genes of eight closely related isolates of serogroup A N. meningitidis (subgroup IV-1) from a recent meningitis epidemic in West Africa. DNA sequence anal. and Southern blot expts. indicated that changes occurred in the opa genes of these bacteria as they spread through the human population, over a relatively short period of time. Such changes in one or a few loci within a clonal population are referred to as microevolution. The distribution of sequences present in hypervariable (HV) regions of the opa genes suggests that duplication of all or part of opa genes into other opa loci changed the repertoire of Opa proteins that could be expressed. Addnl. variability in this gene family appears to have been introduced by horizontal exchange of opa sequences from other meningococcal strains and from Neisseria gonorrhoeae. These results indicate that processes of recombination and genetic exchange contributed to variability in major surface antigens of this clonal population of pathogenic bacteria.

CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 10, 14, 15

IT **Mutation**
(duplication, in gene opa of **Neisseria meningitidis** from meningitis epidemic of human, **surface antigen** microevolution in relation to)

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=> fil wpids
FILE 'WPIDS' ENTERED AT 11:04:17 ON 21 MAR 2002
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FILE LAST UPDATED: 19 MAR 2002              <20020319/UP>
MOST RECENT DERWENT UPDATE            200218   <200218/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

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     (FILE 'HCAPLUS' ENTERED AT 10:58:21 ON 21 MAR 2002)
               DEL HIS Y

     FILE 'WPIDS' ENTERED AT 11:00:27 ON 21 MAR 2002
L1             4 S NHHA OR NH HA OR N HHA
L2           782 S NEISSER?
L3             1 S L1 AND L
L4             1 S L1 AND L2
L5           303 S MENINGITID?
L6             1 S L5 AND L1
L7          1723 S SURFACE (3A) ANTIGEN#
L8             1 S L1 AND L7
L9             1 S L1 AND ANTIGEN#
L10            1 S L4 OR L6 OR L8 OR L9
L11            4 S NHH A
L12            0 S L11 AND (L2 OR L5 OR ANTIGEN#)
L13           22 S L7 AND (L2 OR L5)
L14            9 S L13 (L) (DELET? OR MUTAT? OR MODIF? OR TRUNCAT? OR FRAG?)
L15            8 S L14 NOT L10

     FILE 'WPIDS' ENTERED AT 11:04:17 ON 21 MAR 2002

=> d .wp l10 tech;d .wp tech l15 1-8

L10  ANSWER 1 OF 1  WPIDS COPYRIGHT 2002   DERWENT INFORMATION LTD
AN   2001-488774 [53]   WPIDS
CR   2001-457721 [49]
DNC  C2001-146735
TI   New NhhA surface antigen polypeptides and
     polynucleotides from Neisseria meningitidis, useful in
     producing vaccines for treating or preventing broad spectrum of
     Neisseria meningitidis.
DC   B04 D16
IN   JENNINGS, M P; PEAK, I R A
PA   (UYQU) UNIV QUEENSLAND
CYC  93
PI   WO 2001055182 A1 20010802 (200153)* EN   91p
```

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001028181 A 20010807 (200174)

ADT WO 2001055182 A1 WO 2001-AU69 20010125; AU 2001028181 A AU 2001-28181 20010125

FDT AU 2001028181 A Based on WO 200155182

PRAI US 2000-177917P 20000125

AB WO 200155182 A UPAB: 20011217

NOVELTY - An isolated protein comprising twelve or more contiguous conserved amino acids of an **NhhA** polypeptide, is new. The isolated protein is not a wild-type **NhhA** polypeptide.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated protein comprising a sequence of residues 1-50, 109-120, 135-198, 221-239, or 249-604 of a 604 residue amino acid sequence, fully defined in the specification, where the isolated protein is not a wild type **NhhA** polypeptide;

(2) an allelic variant, fragment or derivative of the isolated protein;

(3) a pharmaceutical composition comprising one or more isolated proteins;

(4) an isolated nucleic acid, encoding the novel polypeptide, or the polypeptide of (1), or (2);

(5) an expression vector which includes the isolated nucleic acid of (4); and

(6) a host cell transformed with the expression vector of (3).

ACTIVITY - Antibacterial.

No biological data is given.

MECHANISM OF ACTION - Vaccine.

USE - The proteins are useful in diagnostics, therapeutic and prophylactic vaccines against a broader spectrum of N. **meningitidis**, and in designing and/or screening of medicaments.

ADVANTAGE - The proteins as a vaccine can effectively immunize against a broader spectrum of N. **meningitidis** strains than would be expected from a corresponding wild-type **surface antigen**.

Dwg.0/14

TECH UPTX: 20010919

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Protein: The protein is capable of eliciting an immune response which is less strain-specific than that elicited by a corresponding said **NhhA** polypeptide, and provides protection against one or more strains of N. **meningitidis**. The isolated protein comprises 20-100 or more contiguous conserved amino acids. The **NhhA** polypeptide has a 594 (AA1), 594 (AA2), 598 (AA3), 598 (AA4), 592 (AA5), 592 (AA6), 586 (AA7), 596 (AA8), 592 (AA9), or 596 (AA10) residue amino acid sequence, all fully defined in the specification. The isolated protein has an amino acid sequence selected comprising:

(a) residues 1-50 of AA1-AA10;
(b) residues 125-188 of AA1 or AA2;
(c) residues 122-185 of AA3, AA5, or AA10;
(d) residues 127-190 of AA4 or AA9;
(e) residues 132-195 of AA6;
(f) residues 131-194 of AA7 or AA8;
(g) residues 211-229 of AA1;
(h) residues 206-224 of AA3;

(i) residues 237-591 of AA1 or AA5;
(j) residues 237-592 of AA2 or AA10;
(k) residues 235-589 of AA3;
(l) residues 239-594 of AA4 or AA9;
(m) residues 244-599 of AA6; or
(n) residues 243-598 of AA7 or AA8.
The isolated protein further comprises one or more variable (V) region amino acids of an **NhhA** polypeptide. The polypeptide fragment is immunogenic.
Preferred Composition: The pharmaceutical composition is a vaccine.
Preferred Nucleic Acid: The isolated nucleic acid has a nucleotide sequence comprising residues 1-150, 325-361, 403-595, 661-717, or 745-1815 of a 1488 base pair sequence, fully defined in the specification. The nucleic acid has a nucleotide sequence selected from a 1539, 1542, 1224, 1302 or 1509 base pair sequence, all fully defined in the specification.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Host Cell: The host cell is a bacterium, preferably **Neisseria meningitides**.

L15 ANSWER 1 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-367614 [38] WPIDS
DNC C2001-112781
TI Immunogenic composition for treating **Neisserial** bacteria infection, has **Neisseria meningitidis** antigens from serogroups B, C with further **Neisserial** proteins and protective antigens against other pathogenic organisms.
DC B04 D16
IN GIULIANI, M M; PIZZA, M; RAPPUOLI, R
PA (CHIR-N) CHIRON SPA
CYC 94
PI WO 2001037863 A2 20010531 (200138)* EN 27p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001018785 A 20010604 (200153)
ADT WO 2001037863 A2 WO 2000-IB1940 20001129; AU 2001018785 A AU 2001-18785 20001129
FDT AU 2001018785 A Based on WO 200137863
PRAI GB 1999-28196 19991129
AB WO 200137863 A UPAB: 20010711
NOVELTY - An immunogenic composition (I) comprising **Neisseria meningitidis** (Nm) serogroup C oligosaccharide and Nm serogroup B outer membrane protein, in combination with proteins (P1) (or its immunogenic **fragments**) and/or protective antigens against Nm serogroups A, W or Y, Hemophilus influenza, Pneumococcus, diphtheria, tetanus, whooping cough, hepatitis B virus and/or Helicobacter pylori, is new.
DETAILED DESCRIPTION - An immunogenic composition (I) comprising **Neisseria meningitidis** (Nm) serogroup C oligosaccharide and Nm serogroup B outer membrane protein, in combination with proteins (P1) (or its immunogenic **fragments**) and/or protective antigens against Nm serogroups A, W or Y, Hemophilus influenza, Pneumococcus, diphtheria, tetanus, whooping cough, hepatitis B virus and/or Helicobacter pylori, is new.

P1, or its immunogenic **fragments**, is disclosed in WO99/57280, WO99/36544, WO99/24578, WO97/28273, WO96/29412, WO95/03413 or WO99/31132.

INDEPENDENT CLAIMS are also included for the following:

(1) an immunogenic composition comprising NmC oligosaccharide and NmB proteins 919, 287 and/or ORF1; and

(2) a vaccine comprising (I).

ACTIVITY - Antibiotic.

MECHANISM OF ACTION - Vaccine.

Groups of guinea pigs received one of NmC conj./alum, NmB/alum, NmC conj./NmB/alum and NmC conj./NmB/MF59 vaccine components. Each animal received two injections, intramuscularly (IM), separated by 28 days. Serum samples were obtained prior to each injection and 18 days after the second injection. Each dose consisted of two 0.25 ml IM injections. Serum samples were assayed for IgG anticapsular antibody concentrations to NmC and for IgG anti-outer membrane vesicle antibody concentrations to NmB by ELISA. A specific anti-meningococcal B antibody response was induced by the vaccine combinations comprising NmB and a specific anti-meningococcal C antibody response was induced by the vaccine combinations comprising NmC. The antibody response induced by the combination of NmC conjugate and NmB in the presence of MF59 adjuvant was significantly greater than the antibody response induced by either the NmC conjugate alone or the combination of the NmC conjugate and NmB in the presence of alum. When the adjuvant MF59 was present, the antibody titer for the combination vaccine increased approximately 6-fold. Serum samples were also tested for complement-mediated bactericidal titers to MenC strain 60E and MenB strain 44/76. The combination vaccine elicited high titers of serum bactericidal antibody for both NmB and NmC. 2-5 fold higher NmB bactericidal titers were obtained with the combination vaccine than with the NmB vaccine alone. The antibodies directed to meningococcal B and C induced by the vaccine combinations comprising NmB and NmC were bactericidal.

USE - (I) is useful for treating or preventing infection due to **Neisserial** bacteria.

Dwg.0/2

TECH UPTX: 20010711

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: The protective antigen is a polysaccharide antigen, diphtheria toxoid, tetanus toxoid, HBV (Hepatitis B virus) **surface antigen** and/or HBV core antigen, CagA, VacA, NAP, HopX, HopY and/or urease, pertussis holotoxin (PT) and filamentous hemagglutinin (FHA), optionally further comprising pertactin and/or agglutinogens 2 or 3. The NmB outer membrane proteins are preferably present as proteoliposomic vesicles. (I) comprises in addition to NmB and NmC proteins, P1 whose amino acid sequences are disclosed in fig 4 or fig 13 of WO97/28273, SEQ.IDs.1-8 disclosed in WO96/29412, SEQ.IDs.1-23 disclosed in WO95/03413, SEQ.ID. 2 disclosed in WO99/31132 or the 45 amino acid sequences defined in WO99/36544. (I) is conjugated to a carrier which is a protein, preferably CRM197 or aluminum hydroxide or MF59.

L15 ANSWER 2 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-281727 [29] WPIDS
DNC C2001-085661
TI Antagonist and adjuvant activity in vaccine preparation for enhancing immune response comprises a lipopolysaccharide isolated from a gram negative bacterium defective in at least msbB or htrB or their analog or derivative.
DC B04 C06 D16
IN CROWLEY, R; HONE, D; SHATA, M
PA (UYMA-N) UNIV MARYLAND BIOTECHNOLOGY INST
CYC 91

PI WO 2001025254 A2 20010412 (200129)* EN 77p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001014311 A 20010510 (200143)
ADT WO 2001025254 A2 WO 2000-US27402 20001004; AU 2001014311 A AU 2001-14311 20001004
FDT AU 2001014311 A Based on WO 200125254
PRAI US 2000-192650P 20000327; US 1999-157635P 19991004
AB WO 200125254 A UPAB: 20010528

NOVELTY - A vaccine preparation, (I), comprising a substantially pure lipopolysaccharide (LPS) antagonist isolated from a gram negative bacterium that is defective in at least one of the msbB or htrB genes or an analog or derivative of the msbB or htrB genes and a vaccine antigen which is not isolated from the gram negative bacterium is new.

DETAILED DESCRIPTION - The vaccine preparation where the LPS antagonist has reduced pyrogenicity relative to an LPS antagonist isolated from the wild type bacterium.

INDEPENDENT CLAIMS are included for:

(1) the preparation of (I);

(2) the induction of an immune response in a subject comprising the administration of (I) to induce an immune response against the vaccine antigen in the subject; and

(3) a kit for inducing an immune reaction against an antigen in a subject, comprising (I) and a vaccine antigen, which is not isolated from the gram negative bacterium.

ACTIVITY - Cytostatic; antiviral; antifungal; antiparasitic; immunosuppressive.

Each vaccine preparation contained 50 mg of the vaccine peptide (Hep-Tat), which corresponds to the heparin binding domain of the HIV-1 regulatory protein Tat, comprising the sequence (GLGIS YGRKKRRQR). The peptide antigen was prepared synthetically as a Multiple Antigen Peptide (MAPS; Genosys). The preparations comprised 50 mg of Hep-Tat and a range of LPS antagonist doses (from 1 mg to 10 mg). The LPS antagonist was isolated from MLK986 cultured at 37 deg. C. Three groups of BAL Blc mice were injected intraperitoneally with a single 50 micro g dose of a preparation. Control groups were injected with 50 micro g of LPS antagonist formulated with alum as an adjuvant. The immunogenicity of each formulation was measured by taking venous blood from the mice in each group before vaccination (A) and 14 days after vaccination (B), and serum prepared. A second 50 micro g vaccination was applied to the appropriate cohort at 21 days and blood collected 7 days later (C). The level of Hep Tat specific IgG was ascertained by ELISA. The dilutions needed to achieve 50 % saturation of the plates are presented: control: (A) less than 10 (B) less than 10 (C) less than 10; 50 micro g Hep-Tat + 1 micro g LPS antagonist: (A) less than 10 (B) 20 (C) 300; 50 micro g Hep-Tat + 3 micro g LPS antagonist: (A) less than 10 (B) 30 (C) 3000; 50 micro g Hep-Tat + 10 micro g LPS antagonist (A) less than 10 (B) 30 (C) 3000; 50 micro g Hep-Tat only: (A) less than 10 (B) less than 10 (C) less than 10.

MECHANISM OF ACTION - Vaccine.

USE - A vaccine adjuvant comprising a LPS antagonist isolated from a gram negative bacterial strain is useful for increasing the immune response to a vaccine. Where the viral antigen is selected from the following group: orthomyxoviruses, retroviruses, herpes viruses, lentiviruses, rhabdoviruses, picornoviruses, poxviruses, rotaviruses and parvoviruses, preferably from influenza virus, RSV, EBV, CMV, herpes simplex virus, human immunodeficiency virus, rabies, poliovirus and

vaccinia and preferably from a group consisting of human immuno deficiency virus antigens Nef, p24, gp120, gp41, Tat, Rev and Pol, T cell and B cell epitopes of gp120, the hepatitis B **surface antigen**, rotavirus **antigens** VP4 and VP7, influenza virus antigens hemagglutinin or nucleoprotein and herpes simplex virus thymidine kinase. The bacterial pathogen is selected from a group consisting of Mycobacterium spp., Helibacter pylori, Salmonella spp.,Shigella spp., E. coli, Rickettsia spp., Listeria spp., Legionella pneumoniae, Pseudomonas spp., Vibrio spp. and Borellia burgdorferi, preferably the capsular polysaccharide of **Neisseria** meningitis, the Vi polysaccharide of Salmonella enterica typhi, Shigella sonnei form 1 antigen, the O antigen of V. cholerae Inaba strain 569, the cholera toxin or TCP of V. cholerae, CFA/I fimbrial antigen of enterotoxigenic or the heat labile toxin of E. coli, pertactin or adenylate cyclase-hemolysin of Bordetella pertussis and **fragment** C of tetanus toxin of Clostridium tetani.

The vaccine antigen is derived from a parasitic pathogen selected from the group consisting of Plasmodium spp., Trypanosome spp., Giardia spp. , Boophilus spp., Babesia spp., Entamoeba spp. , Eimeria spp., Leishmania spp., Schistome spp. Brugia spp., Fascida spp., Dirofilaria spp., Wucheria spp. Onchocerea spp., preferably from the group consisting of the circumsporozoite antigen of P. berghei and P. falciparum, the merozoite **surface antigen** of Plasmodium spp. the galactose specific lectin of Entamoeba histolytica, gp63 of Leishmania spp., paramyosin of Brugia malayi, the triose phosphate isomerase of Schistosoma mansoni, the secreted globin like protein of Trichostrongylus colubriformis the glutathione-S transferase of Fraciola hepatica, Schistosoma bovis and S. japonicum and KLH of Shistosoma bovi and another not given in the specification. (I) where the antigen elicits an immune reaction against a tumor antigen, preferably selected from prostate specific antigen, TAG-72, carcinoembrionic antigen (CEA), MAGE 1, tyrosinase and mutant p53 antigen. (I) where the antigen elicits an immune reaction against the CD3 receptor T cells or against an autoimmune antigen preferably IAS beta chain. (I) where the antigen elicits an immune reaction against an immuno stimulatory molecule selected from the group consisting of M-CSF, GM-CSF, IL-4, IL-5, IL-6, IL-10, IL-12 and IFN- gamma . Diseases and disorders that can be treated include viral, fungal and parasitic, infections, cancers and autoimmune diseases in fowl and all mammals, preferably humans.

ADVANTAGE - The invention provides LPS, lipid A or their derivatives which are effective as adjuvants or antagonists and lack pyrogenic activity.

Dwg.0/3

TECH UPTX: 20010528

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: Each vaccine preparation contained 50 mg of the vaccine peptide. The peptide antigen was prepared synthetically as a Multiple Antigen Peptide (MAPS; Genosys).

Preferred Vaccine: (I) where the LPS agonist comprises a LPS molecule or a lipid A molecule or a heterologous mixture of the two. The LPS antagonist inhibits an activity of a wildtype LPS by at least a factor of 102, has pyrogenicity that is 105 lower than that of wildtype LPS, increases an immune response to the antigen in a host at least 103 fold, relative to an immune response to the antigen administered to the host in the absence of the antagonist and comprising administering to the subject a vaccine antigen and a substantially pure preparation of an LPS antagonist. The vaccine antigen is a polysaccharide, a peptide or protein or a nucleic acid. The vaccine antigen elicits an immune reaction against a viral antigen. The vaccine antigen elicits an immune reaction against a bacterial pathogen. The vaccine antigen is derived from a parasitic pathogen.

L15 ANSWER 3 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-687261 [67] WPIDS
DNC C2000-209150
TI Composition having genetically **modified** live oral commensal bacteria which express immunogenic **fragments** of mucosal pathogens, used as oral vaccines to treat host against Bordetella pertussis, poliovirus infection.
DC B04 D16
IN HALPERIN, S A; LEE, S F
PA (UYDA-N) UNIV DALHOUSIE
CYC 92
PI WO 2000064457 A1 20001102 (200067)* EN 52p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000044853 A 20001110 (200109)
ADT WO 2000064457 A1 WO 2000-US10954 20000421; AU 2000044853 A AU 2000-44853 20000421
FDT AU 2000044853 A Based on WO 200064457
PRAI US 1999-298135 19990423
AB WO 200064457 A UPAB: 20001223
NOVELTY - A composition (I) for stimulating protection against infection by a pathogen, comprising a live commensal oral organism (II) genetically **modified** to express multiple immunogenic **fragments** of the pathogen, is new.

ACTIVITY - Antibacterial; antiviral.

MECHANISM OF ACTION - Vaccine.

The biological activity of the immunogenic **fragment** of pertussis toxin (PT) comprising N-terminal 179 amino acids of the S1 subunit of PT was tested in mice by leukocytosis promoting and histamine sensitizing assays. A cohort of BALB/c female mice were immunized intraperitoneally with heat killed S. gordonii RJMIII cells. The animals were boosted with freshly prepared heat-killed cells 2 and 3 weeks later. A cohort of non-immunized mice were used as a control. At 7 days after the last booster, sera were obtained from the animals. The immunized mice had a titer of 12,800 against the native PT by enzyme linked immunosorbent assay (ELISA). Each animal from the immunized and control groups was then injected intraperitoneally with 0.5 micro g of native PT. The total leukocyte (WBC) count was determined before and after PT injection. Before PT challenge, the control and immunized mice had average WBC counts of 9.14 multiply 109/ liter and 8.28 multiply 109/liter, respectively. Three days after PT injection the control mice had an average WBC count of 29.8 multiply 109/liter, 3.3 times higher than that before PT challenge. The average WBC count of the immunized mice was 11.5 multiply 109/liter after PT injection, 1.4 times higher than that before the challenge. Each animal was further given 2 mg of histamine diphosphate i.e. 4 days after PT challenge, and deaths within 24 hours of histamine administration were recorded. All five of the immunized mice survived the treatment, while only one of the six control mice survived. These results strongly suggested that the recombinant S1 **fragment** expressed S. gordinii can induce protective antibodies in vivo.

USE - (I) which is administered orally or intranasally, is used for prophylactically treating a host against infection by a pathogen such as Bordetella pertussis, respiratory syncitial virus, poliovirus, Mycoplasma pneumoniae, meningococcus, pneumococcus, rotavirus, influenza, parainfluenza, Corynebacterium diphtheriae, Clostridium tetani, hepatitis B virus, **Neisseria** gonorrhoeae non-typeable Haemophilus

influenzae Chlamydia pneumoniae, Chlamydia trachomatis, Moraxella catarrhalis, or their combinations. (I) is also used for chronic immunization of a host against infection by a pathogen. (All claimed).

ADVANTAGE - The immunogenic **fragments** contained in (I) are non-toxic to a host receiving the composition as well as the oral commensal organism that is used as the carrier of the immunogenic **fragment**. As oral Streptococci are known to be transmitted from mother to child through saliva, immunized mother may transmit the vaccine strain to their babies. This natural means of inoculation provides immunity in undeveloped countries where conventional vaccines are too expensive to be effectively used. The live oral vaccines have the properties of simplicity in administration and the potential for eliminating the local discomfort (redness and swelling) and systemic manifestations, (fever, headache and malaise) that commonly result from conventional vaccination. The mucosal immune response of the host is long term because the antigens required to continuously provide the stimulation necessary to maintain the mucosal immune response are continuously expressed by the live **modified** organism colonizing the oral cavity of the host, so that subsequent or repeated inoculation is minimized or unnecessary once the colonization of the oral mucosal has been well established.

DESCRIPTION OF DRAWING(S) - The figure shows the preparation of a plasmid useful for obtaining a live commensal organism genetically **modified** to express an immunogenic **fragment** of the S1 subunit of pertussis toxin.

Dwg.1A/2

TECH UPTX: 20001223

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: The multiple immunogenic **fragments** of (I) are derived from the same, or one or more mucosal pathogens such as Bordetella pertussis, respiratory syncitial virus, poliovirus, Mycoplasma pneumoniae, meningococcus, pneumococcus, rotavirus, influenza, parainfluenza, Corynebacterium diphtheriae, Clostridium tetani, hepatitis B virus, **Neisseria** gonorrhoeae non-typeable Hemophilus influenzae Chlamydia pneumoniae, Chlamydia trachomatis, Moraxella catarrhalis, or their combinations. The immunogenic **fragment** is derived from pertussis toxin, and comprises the N-terminal 179 amino acids of the S1 subunit of the pertussis toxin. Alternatively, the immunogenic **fragment** is derived from one or more pertussis toxin, filamentous hemagluttinin, pertactin or fimbriae. (II) is Streptococcus such as S. gordonii, S. salivarius or S. mitis. The genetic **modification** comprises transmission of the S. gordonii with a vector encoding the **surface** protein **antigen** P1 of S. mutans, in which a sequence encoding the **surface** protein **antigen** is **modified** by inserting a sequence encoding the immunogenic **fragment**. (II) is further **modified** to express a mucosal adjuvant. (I) further comprises an immunological adjuvant.

L15 ANSWER 4 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-594517 [56] WPIDS
CR 2000-594515 [55]; 2000-594516 [55]; 2000-679550 [64]; 2001-006956 [61]
DNC C2000-177617
TI A Streptococcus pneumoniae vaccine for preventing pneumonia and meningitis comprises a polysaccharide antigen conjugated to protein D from Haemophilus influenzae.
DC B04 D16
IN CAPIAU, C; DESCHAMPS, M; DESMONS, P M; LAFERRIERE, C A J; POOLMAN, J; PRIEELS, J
PA (SMIK) SMITHKLINE BEECHAM BIOLOGICALS
CYC 93

PI WO 2000056360 A2 20000928 (200056)* EN 77p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000034307 A 20001009 (200103)
BR 2000009163 A 20011226 (200206)
EP 1163000 A2 20011219 (200206) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

ADT WO 2000056360 A2 WO 2000-EP2468 20000317; AU 2000034307 A AU 2000-34307 20000317; BR 2000009163 A BR 2000-9163 20000317, WO 2000-EP2468 20000317; EP 1163000 A2 EP 2000-912626 20000317, WO 2000-EP2468 20000317

FDT AU 2000034307 A Based on WO 200056360; BR 2000009163 A Based on WO 200056360; EP 1163000 A2 Based on WO 200056360

PRAI GB 1999-16677 19990715; GB 1999-6437 19990319; GB 1999-9077 19990420; GB 1999-9466 19990423

AB WO 200056360 A UPAB: 20020128
NOVELTY - A polysaccharide conjugate antigen (I) comprising a polysaccharide antigen derived from a pathogenic bacterium conjugated to protein D (or a **fragment**) from Haemophilus influenzae, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an immunogenic composition comprising (I);
(2) an immunogenic composition comprising **Neisseria meningitidis** protein D polysaccharide conjugate antigen;
(3) an immunogenic composition comprising Haemophilus influenzae b protein D polysaccharide conjugate antigen;
(4) an immunogenic composition comprising conjugated capsular polysaccharides of Streptococcus pneumoniae, Haemophilus influenzae b , meningococcus C and meningococcus Y, the carrier protein for at least one of the polysaccharides is protein D from H. influenzae;
(5) a vaccine comprising (1)-(4); and
(6) a method for producing an immunogenic composition to a pathogenic bacterium comprising:
(a) isolating a polysaccharide antigen from a pathogenic bacterium;
(b) activating the polysaccharide; and
(c) conjugating the polysaccharide to protein D.
ACTIVITY - Antibacterial. No biological data given
MECHANISM OF ACTION - Vaccine.
USE - The bacterial polysaccharide antigen vaccines are used to induce an immune response to Streptococcus pneumoniae and is used to prevent pneumonia, bacteremia, meningitis and acute otitis media.
ADVANTAGE - The conjugation of the antigen to a larger immunogenic protein increases the induced immune response, especially in children less than two years old.
Dwg.0/3

TECH UPTX: 20001106
TECHNOLOGY FOCUS - BIOLOGY - Preferred Polysaccharide Conjugate: In (I) the antigen is a Vi polysaccharide from Salmonella typhi, a meningococcal polysaccharide, a (**modified** polysaccharide) from a group B meningococcus, a polysaccharide from , Streptococcus agalactidae, S. pneumoniae, Staphylococcus aureus, Mycobacteria or Cryptococcus neoformans, a lipopolysaccharide of non-typeable Haemophilus influenzae, Moraxella catharralis or Shigella sonnei, a capsular polysaccharide from H. influenzae or the lipopeptidophosphoglycan of Trypanosma cruzi. The polysaccharide antigen in derived from **Neisseria meningitidis** serotypes A, C or Y. The protein D conjugate antigen

is adsorbed onto aluminum phosphate.
Preferred Immunogenic Composition: The composition comprises S. pneumoniae polysaccharide antigens from at least four serotypes and additionally at least one S. pneumoniae protein antigen. The protein **antigen** is an outer **surface** protein, toxin, adhesin, lipoprotein or secreted protein, especially pneumolysin, PspA, PspC, PsaA, CbpA or their transmembrane **deletion** variants or glyceraldehyde-3-phosphate dehydrogenase. The polysaccharide antigens are conjugated to protein D with the polysaccharide from H. influenzae b conjugated to tetanus toxoid. the composition further comprises a adjuvant which is a preferential inducer of a TH1 response and is especially 3D-MPL, a saponin immunostimulant or an immunostimulatory Cpg oligonucleotide.
Preparation: A polysaccharide C-protein D conjugate was bulk adsorbed onto aluminum sulfate-WAP by stirring for 5 minutes at room temperature. The pH was adjusted to 5.1 and the mixture stirred for a further 18 hours. Sodium chloride was added to 150 mM and the mixture stirred for 5 minutes at room temperature. 2-phenoxyethanol was added to 5 mg/ml, the mixture stirred for a further 15 minutes at room temperature and then adjusted to pH 6.1.

L15 ANSWER 5 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-532863 [48] WPIDS
DNC C2000-158762
TI New vaccine compositions comprising pathogenic bacteria which contain a **mutation** affecting DNA adenine methylase, useful for treating or preventing bacterial infection, especially Salmonella infection, in humans and domestic animals.
DC B04 D16
IN HEITHOFF, D M; LOW, D A; MAHAN, M; SINSHEIMER, R L; MAHAN, M J
PA (REGC) UNIV CALIFORNIA
CYC 91
PI WO 2000045840 A1 20000810 (200048)* EN 111p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000032221 A 20000825 (200059)
EP 1150711 A1 20011107 (200168) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
BR 2000007966 A 20011106 (200175)
ADT WO 2000045840 A1 WO 2000-US2866 20000202; AU 2000032221 A AU 2000-32221 20000202; EP 1150711 A1 EP 2000-910070 20000202, WO 2000-US2866 20000202; BR 2000007966 A BR 2000-7966 20000202, WO 2000-US2866 20000202
FDT AU 2000032221 A Based on WO 200045840; EP 1150711 A1 Based on WO 200045840; BR 2000007966 A Based on WO 200045840
PRAI US 2000-495614 20000201; US 1999-241951 19990202; US 1999-305603 19990505
AB WO 200045840 A UPAB: 20010410
NOVELTY - Vaccine compositions comprising pathogenic bacteria (e.g. Salmonella) which contain a **mutation** affecting DNA adenine methylase (Dam), are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are provided for the following:
(1) an immunogenic composition (I) comprising live attenuated pathogenic bacteria containing a **mutation** which alters Dam activity such that the pathogenic bacteria are attenuated;
(2) a kit comprising (I);
(3) an immunogenic composition (II) comprising killed pathogenic bacteria containing a **mutation** which alters Dam activity;

(4) an attenuated strain (AS1) of a pathogenic bacteria containing a **mutation** which alters Dam activity such that the bacteria are attenuated;

(5) a method of eliciting an immune response in an individual, comprising administering (I);

(6) a method of preventing or treating infection by pathogenic bacteria, comprising administering (I) in an amount sufficient to reduce a symptom associated with infection by the pathogenic bacteria;

(7) a method of treating an individual infected with a pathogenic bacteria, comprising administering a composition comprising an agent which alters Dam activity;

(8) a method of eliciting an immune response against a second species of Salmonella in an individual, comprising administering an immunogenic composition comprising an attenuated first species of Salmonella which contains a **mutation** that alters Dam activity such that it becomes attenuated;

(9) a method of identifying an agent which may have antibacterial activity, comprising:

(a) using an in vitro transcription system to detect an agent which alters the level of transcription from a Dam gene when the agent is added to the transcription system;

(b) identifying an agent having antibacterial activity by its ability to alter the level of transcription when compared to the level of transcription when no agent is added;

(10) a method of identifying an agent which may have antibacterial activity, comprising:

(a) using an in vitro translation system to detect an agent which alters the level of translation from an RNA transcript encoding Dam when the agent is added to the system;

(b) identifying an agent having antibacterial activity by its ability to alter the level of translation from the RNA transcript when compared to the level of translation when no agent is added;

(11) a method of identifying an agent which may have antibacterial activity comprising determining whether the agent binds to Dam, where an agent that binds to Dam has antibacterial activity;

(12) a method of identifying an agent which may have antibacterial activity, comprising:

(a) incubating non-methylated oligonucleotides comprising a Dam binding site with Dam, S-adenosyl methionine, and an agent, where the non-methylated oligonucleotide further comprises a signal;

(b) digesting all non-methylated target sites, therefore releasing the non-methylated oligonucleotides; and

(c) detecting inhibition of DNA adenine methylase as an increase in the signal due to digestion of the non-methylated target sites, where an agent is identified by its ability to cause an increase in signal compared to conducting steps (a), (b), and (c) in absence of agent;

(13) a method of identifying an agent which may have antibacterial activity, comprising:

(a) contacting an agent to be tested with a suitable host cell that has Dam function; and

(b) analyzing at least one characteristic which is associated with alteration of Dam function, where an agent is identified by its ability to elicit at least one characteristic;

(14) a method of preparing (I), comprising combining an excipient with pathogenic bacteria containing a **mutation** which alters Dam activity such that the pathogenic bacteria are attenuated; and

(15) a method for preparing attenuated bacteria capable of eliciting an immunological response by a host susceptible to disease caused by the corresponding or similar pathogenic microorganism, comprising constructing at least one **mutation** in the pathogenic bacteria which results

in altered Dam function.

ACTIVITY - Antibacterial; immunostimulant.

MECHANISM OF ACTION - Vaccine.

BALB/c mice were perorally immunized via gastrointubation with a dose of 109 Dam- S. typhimurium. Five weeks later, the immunized mice were challenged perorally with 109 wild-type S. typhimurium. After five weeks, surviving mice were challenged with the wild-type 14028 strain. Survival for four weeks post challenge was deemed full protection.

The results show that all (17/17) mice immunized with a S. typhimurium Dam- insertion strain survived a wild-type challenge of 104 above the LD50, while all non-immunized mice (12/12) died following challenge. Virtually no visible effects of typhoid fever were observed subsequent to immunization with Dam- Salmonella, nor were there visible effects after the wild type challenge.

Moreover, because all (8/8) mice immunized with Salmonella containing the nonpolar Dam deletion survived challenge, these data indicate that protection was specifically due to the absence of Dam protein.

USE - The vaccine compositions are useful for eliciting an immune response, and/or treating or preventing disease associated with bacterial infection, especially Salmonella infection, in humans and domestic animals.

Dwg.0/8

TECH UPTX: 20001001

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: In (I), the **mutation** reduces, preferably eliminates, Dam activity. The **mutation** is a **deletion** of the Dam gene. Alternatively, the **mutation** causes an increase in expression of Dam. The pathogenic bacteria are Salmonella (e.g. S. typhimurium (preferred), S. enteritidis (preferred), S. typhi, S. abortus-ovi, S. abortus-equi, S. dublin (preferred), S. gallinarum, or S. pullorum), Escherichia (e.g. E. coli), Vibrio (e.g. V. cholerae), Yersinia (e.g. Y. psuedotubercolosis), Shigella, Haemophilus, Bordetella, **Neisseria**, Pasteurella or Treponema. (I) further comprises a heterologous antigen. The pathogenic bacteria further contain an expression cassette comprising a polynucleotide sequence encoding a heterologous antigen. The **mutation** is non-reverting. The bacteria contain a second **mutation** which causes attenuation of the bacteria.

In (II), the **mutation** is nonlethal and renders the pathogenic bacteria attenuated or lethal. The pathogenic bacteria are Salmonella. The **mutation deletes** Dam gene or causes over-expression of Dam gene.

Preferred Method: In the method of (5), the immune response persists more than four weeks after administration. The individual is a human, or a domestic animal such as a chicken or a cow. In the method of (6), the bacterial infection is a Salmonella infection and the pathogenic bacteria used in (I) are Salmonella. In the method of (8), the first Salmonella species is S. typhimurium or S. enteritis. In the method of (9), (10) and (11), the Dam gene is from Salmonella.

In the method of (12), the oligonucleotides are tethered to a solid surface. The solid surface is a microtiter plate containing avidin and the oligonucleotide comprises biotin. The Dam binding site is a GATC sequence. The Dam is from Salmonella. The agent is selected from an inhibitor library consisting of the polypeptides, organic compounds or inorganic compounds. In the method of (13), the host cell is Salmonella.

In the method of (15), a first **mutation** is introduced into a Dam gene. A second **mutation** is created in a gene that is independent of the first **mutation**, where the second **mutation** causes attenuation of the pathogenic bacteria. The first **mutation** eliminates expression of Dam. The method further comprises inserting an expression cassette, comprising one or more structural genes coding for a

desired antigen, into the attenuated bacteria. The desired antigen is **Fragment** C of tetanus toxin, the B subunit of cholera toxin, the hepatitis B **surface antigen**, Vibrio cholerae lipopolysaccharide (LPS), human immunodeficiency virus antigens and Shigella soneii LPS.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Strain: In AS1, the **mutation** reduces, preferably eliminates, Dam activity. The **mutation** is a **deletion** of the Dam gene. Alternatively, the **mutation** causes an increase in expression of Dam. The bacteria are Salmonella.

L15 ANSWER 6 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-412285 [35] WPIDS
DNN N2000-308159 DNC C2000-125012
TI Hepatitis B virus core antigen particles with multiple, variable immunogenicities useful as vaccines for the treatment of a range of diseases, e.g. mumps, malaria and hepatitis.
DC B04 D16 S03
IN MURRAY, K
PA (BIOJ) BIOGEN INC
CYC 91
PI WO 2000032625 A1 20000608 (200035)* EN 55p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000018417 A 20000619 (200044)
BR 9915942 A 20010821 (200155)
EP 1135408 A1 20010926 (200157) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
NO 2001002760 A 20010806 (200157)
CZ 2001001907 A3 20020116 (200215)
KR 2001081068 A 20010825 (200215)
ADT WO 2000032625 A1 WO 1999-US28755 19991203; AU 2000018417 A AU 2000-18417 19991203; BR 9915942 A BR 1999-15942 19991203, WO 1999-US28755 19991203; EP 1135408 A1 EP 1999-961935 19991203, WO 1999-US28755 19991203; NO 2001002760 A WO 1999-US28755 19991203, NO 2001-2760 20010605; CZ 2001001907 A3 WO 1999-US28755 19991203, CZ 2001-1907 19991203; KR 2001081068 A KR 2001-706985 20010604
FDT AU 2000018417 A Based on WO 200032625; BR 9915942 A Based on WO 200032625; EP 1135408 A1 Based on WO 200032625; CZ 2001001907 A3 Based on WO 200032625
PRAI US 1998-110911P 19981204
AB WO 200032625 A UPAB: 20000725
NOVELTY - A HBV (hepatitis B virus) core antigen particle (I) comprising at least 1 capsid binding immunogen (CBI), is new. The CBI comprises at least 1 HBV capsid binding-peptide component (CBC) and at least 1 immunogenic component.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(i) a vaccine (II) comprising (I);

(ii) a method (III) for producing an immune response in an individual, comprising administering (I);

(iii) a method (IV) for increasing the immunogenicity of an immunogen by linking it to a HBV core antigen particle through a HBV capsid-binding peptide;

(iv) a method (V) for detecting the presence of antibodies to an immunogen in a sample, comprising:

(a) contacting the sample with (I) (in which the CBI comprises a diagnostic label or a chemical marker) and allowing any antibodies in the sample to form a complex the CBI; and

(b) detecting the complex formed between the CBI and the antibodies in the sample; and

(v) a HBV CBI (VI) comprising at least 1 (CBC) and at least 1 immunogenic component.

ACTIVITY - Variable, depending on the type of antigens contained in (I).

MECHANISM OF ACTION - Vaccine.

No biological data given.

USE - (I) may be used as a delivery system for a diverse range of immunogenic epitopes, including HBV capsid binding peptides (i.e. they may be used as platforms for presenting immunogens of interest to the immune system). They may also be used as diagnostic reagents. They may be used to vaccinate against a range of diseases (e.g. human immunodeficiency virus (HIV) infections, yellow fever, mumps, hepatitis and malaria) depending on their antigenic properties.

ADVANTAGE - (I) comprises HBV capsid binding peptides which inhibit and interfere with HBV viral assembly by blocking interactions between HBV core proteins and HBV surface proteins. Mixtures of different immunogens and/or capsid binding peptide ligands may be cross linked to the same HBV core particle to produce multicomponent, multivalent HBV core particles that may be used as therapeutic and prophylactic vaccines.

Dwg.0/2

TECH UPTX: 20000725

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Antigens: In (I), the CBI (i.e. (VI)) is orientated on the particle so that it permits the immunogenic component to elicit an immune response when the (I) is administered to an individual. The CBI is linked to the particle via any amino acid residue of the HBV CBC. The CBI is linked to the particle through the amino terminus or carboxy terminus of the HBV CBC. Alternatively, the CBI is linked to the particle via any amino acid residue (or other residue, especially a carbohydrate) of the immunogenic component. The CBI is cross linked to the particle by a crosslinker. The immunogenic component is linked to the amino terminus or carboxy terminus of the HBV CBC directly or via a linker sequence. Preferably they are linked by a multifunctional cross-linker. The multifunctional cross-linker is selected from 1-ethyl-3-(3-dimethylaminopropyl) carbodimide hydrochloride and N-hydroxy-sulphosuccinimide. The immunogenic component comprises 1 or more epitopes that are either immunologic epitopes, immunogenic epitopes and/or antigenic epitopes. They may be linear, conformational, single and/or mixed epitopes. The immunogenic components are either antigens, allergens (animal allergens, insect allergens, plant allergens, atmospheric allergens and/or inhalant allergens), antigenic determinants, proteins, glycoproteins, antibodies, antibody **fragments**, peptides, peptide mimotopes which mimic an antigen or antigenic determinant, polypeptides, glycopeptides, carbohydrates, oligosaccharides, polysaccharides, oligonucleotides and/or polynucleotides. Preferably, the immunogenic component is targeted to or derived from a pathogenic agent (e.g. viruses, mycobacteria, bacteria, bacilli, fungi, protozoa, plants, phages, animal cells or plant cell). The virus is either a retrovirus, herpes virus, orthomyxoviruses, paramyxoviruses, hepadnaviruses, flaviviruses, picornaviruses, papoviruses, adenoviruses, baculoviruses, hantaviruses, parvoviruses, enteroviruses, rhinoviruses, tumor viruses, DNA viruses, RNA viruses, togaviruses, rhabdoviruses and poxviruses. The virus is either human immunodeficiency virus (HIV) type 1 or 2, T cell-leukemia virus, herpes

simplex virus (HSV) type 1 or 2 virus, Varicella-Zoster virus, cytomegalovirus, Epstein-Barr virus, influenza A, B or C virus, respiratory syncytial virus, measles-like virus, mumps virus, parainfluenza virus, hepatitis A, B, C or E virus, yellow fever virus, malaria, dengue virus, tick-borne encephalitis virus, oncovirus, poliomyelitis virus, papillomavirus, rubella virus, rabies virus and/or vaccinia virus. The immunogenic component may also be targeted to or derived from bacillus, enterobacteria, clostridium, Listeria, mycobacterium, Pseudomonas, staphylococcus, eubacteria, mycoplasma, Chlamydia, spirochetes, **Neisseria** and/or salmonella. Preferably, the immunogenic component is targeted to diphtheria, tetanus, acellular pertussis, haemophilus influenza, polio, measles, mumps, rubella, varicella, hepatitis B virus, hepatitis A virus, pneumococcal pneumonia, yellow fever, malaria, hepatitis B virus, hepatitis A virus, typhoid fever, meningococcal encephalitis or cholera.

In (I), the HBV core antigen is an HBV core antigen fusion protein comprising an immunologic epitope, an immunogenic epitope or an antigenic epitope fused to HBV core antigens directly or through a linker sequence to the amino terminus or carboxy terminus of the HBV core antigen. Preferably, the HBV core antigen fusion protein comprises a **truncated** HBV core **antigen**, especially a **surface antigen** (or **fragments**), and comprises a sequence selected from the pre-S1 region, the pre-S2 region and/or the immunodominant a region of a HBV **surface antigen** (or **fragments**). Alternatively, it may be a full length HBV core antigen polypeptide (or portions, **truncates**, **mutations** and/or derivative of them) which are capable of assembling in particulate form. The HBV CBC is selected from:

SLLGRMKGA;
GSLLGRMKGA;
DGSLLGRMKGAA;
ADGSLLGRMKGAAG;
SLLGRMKG (beta-A)C;
RSLLGRMKGA;
HRSLLGRMKGA;
ALLGRMKG;
MHRSLLGRMKGA;
RSLLGRMKGA(beta-A)C; and/or
MHRSLLGRMKGAG(beta-A)GC.

The CBI comprises a diagnostic label or a chemical marker.

Preparation: (I) may be prepared by standard methodologies.

L15 ANSWER 7 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-329926 [29] WPIDS
DNC C2000-100064
TI New carrier material coated with specific antibodies, used to remove tumor necrosis factor and other disease-associated compounds from blood, for treating arthritis or pyelonephritis.
DC A96 B04 D16 P34
IN DUNZENDORFER, U; WILL, G
PA (DUNZ-I) DUNZENDORFER U; (WILL-I) WILL G
CYC 26
PI DE 19845286 A1 20000427 (200029)* 30p
EP 1004598 A2 20000531 (200031) DE
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2001276217 A 20011009 (200174)# 31p
ADT DE 19845286 A1 DE 1998-19845286 19981001; EP 1004598 A2 EP 1999-118541 19990918; JP 2001276217 A JP 2000-102606 20000404
PRAI DE 1998-19845286 19981001; JP 2000-102606 20000404

AB DE 19845286 A UPAB: 20000617
NOVELTY - A carrier material (I), is new and has a coating that comprises antibodies (Ab1) against tumor necrosis factor (TNF) and/or anti-TNF (or their **fragments**) or against TNF-transport proteins and additional antibodies (Ab2) against specific pathogens.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a column (II), for washing blood or plasma, filled with (I) for removal of antigens that cause disease.

ACTIVITY - Antiarthritic; antibacterial; virucide; antiinflammatory; cytostatic.

MECHANISM OF ACTION - Selective removal of disease-related compounds by antigen-antibody reaction.

USE - (I), in the form of a packed column (II), is used extracorporeally to treat blood, plasma or tissues, in cases of any disease which is associated with a specific pathogen, growth factor, protein, peptide, toxin, enzyme, hormone, receptor/tissue marker or cytokine and for which specific antibodies are available. Diseases that may be treated are pyelonephritis, colitis, rheumatoid arthritis, multiple sclerosis, chronic glomerulonephritis, hepatitis B infection, transplant rejection and chronic bronchitis, cancers and circulatory disorders.

Patients with rheumatoid arthritis who did not respond to treatment with methotrexate and cortisone were treated by plasmapheresis, using a column carrying immobilized antibodies against TNF alpha , protein A and beta -Streptococcus A. Over an 84-day period, the mean plasma levels of TNF alpha were reduced from 0.518 to 0.096 mu g/ml, with response rate 59% and the reduction in C-reactive protein 87%.

ADVANTAGE - (I) removes the disease-associated compounds selectively, leaving other plasma components unaltered, eliminating the need to replenish essential plasma factors (as may be necessary in conventional plasmapheresis methods).

Dwg.0/1

TECH UPTX: 20000617
TECHNOLOGY FOCUS - BIOLOGY - Preferred Antibodies: Ab2 are directed against a very wide range of antigens (more than 100, including many mixtures, are listed). Typical of these are (i) a mixture of bacteria and viruses (Staphylococcus aureus, Streptococcus mitis, Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae, K. ozeanae, Staphylococcus pyogenes, Staphylococcus viridans, **Neisseria** cattarhalis, Escherichia coli beta-hemolytic streptococci, hepatitis A **antigen** and hepatitis B **surface antigen**); (ii) beta-hemolytic streptococci and viral capsids; (iii) Streptococcus pneumoniae polysaccharides, viral capsids, Chlamydia and Mycoplasma; (iv) reverse transcriptase and hepatitis A and/or B antigens; (v) human reverse transcriptase and (a) CD20 of B cells or (b) CD2, 3, 5 and 7 of T cells plus epithelial specific antigen; (vi) endothelin (vascular endothelial growth factor, VEGF), or its **fragments** or receptor antagonists, vascular cell adhesion molecule (VCAM), human leucocyte antigen (HLA) and human leucocytes; (vii) soluble Plasmodium falciparum antigen, VCAM, glycate end-product receptors and hemozoin; (viii) Mycobacterium tuberculosis and BCG antigen; (ix) bile acids, ammonia and bilirubin; (x) interleukin-8. Ab2 may be mono- or poly-clonal. Ab1 are particularly directed against TNF.

Preferred Materials: The carrier is plastic, a plastic-coated metal, glass, cellulose material, starch (or its aggregates) or Sepharose (or its derivatives). Ab are bound to the carrier by adsorption or covalently, and may be used as **fragments**. The mixture comprises 1 - 95 weight % Ab1 and the remainder Ab2.

Preferred Apparatus: (I) is coated on the inner wall of (II) or (II) is packed with beads of (I).

TECHNOLOGY FOCUS - POLYMERS - Preferred Carrier Material: Suitable

polymers for the carrier are polyolefin, polyester, polyether, polyamide, polyimide, polyurethane, poly(vinyl chloride), polystyrene, polysulfone, poly(meth)acrylate, polypropylene, poly(vinyl pyrrolidone), fluoro-polymers (or any mixture, derivative or co-polymer of them) or is silicone rubber. Particularly the polymeric carrier has polar properties and its surface is treated with an adhesion promoter, specifically cyanogen bromide, thiophosphine or thionyl chloride.

L15 ANSWER 8 OF 8 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-292988 [25] WPIDS
CR 2000-292989 [25]
DNC C2000-088521
TI New composition comprising isolated Invaplex of gram-negative bacteria comprising at least one invasin protein associated with LPS of the gram-negative bacteria.
DC B04 D16
IN OAKS, E W; ROSS, K; OAKS, E V; TURBYFILL, K R
PA (REED-N) REED ARMY INST RES WALTER; (OAKS-I) OAKS E W; (ROSS-I) ROSS K; (USSA) US SEC OF ARMY
CYC 82
PI WO 2000018354 A2 20000406 (200025)* EN 72p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 2000010984 A 20000417 (200035)
US 6245892 B1 20010612 (200135)
US 2001009957 A1 20010726 (200146)
ADT WO 2000018354 A2 WO 1999-US22771 19990929; AU 2000010984 A AU 2000-10984 19990929; US 6245892 B1 Provisional US 1998-102397P 19980930, Provisional US 1998-102398P 19980930, Provisional US 1999-136190P 19990527, US 1999-408011 19990929; US 2001009957 A1 Provisional US 1998-102397P 19980930, Provisional US 1998-102398P 19980930, Provisional US 1999-136190P 19990527, Div ex US 1999-408011 19990929, US 2001-772878 20010131
FDT AU 2000010984 A Based on WO 200018354
PRAI US 1999-136190P 19990527; US 1998-102397P 19980930; US 1998-102398P 19980930; US 1999-408011 19990929; US 2001-772878 20010131
AB WO 200018354 A UPAB: 20010815
NOVELTY - A composition is new and comprises an isolated Invaplex of gram-negative bacteria comprising at least one invasin protein associated with lipopolysaccharide (LPS) of the gram-negative bacteria.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) preparing isolated Invaplex from Shigella comprising:
(a) water extracting Shigella;
(b) separating and discarding membrane **fragments** from the water extracted from Shigella resulting in a solution containing the Invaplex; and
(c) isolating the Invaplex from the solution;
(2) preparing isolated Invaplex from Escherichia comprising:
(i) water extracting Escherichia;
(ii) separating and discarding membrane **fragments** from the water extracted Escherichia resulting in a solution containing Invaplex; and
(iii) isolating the Invaplex from the solution;
(3) screening agents or drugs which reduce or eliminate Invaplex virulence comprising detecting a dissociation of the Invaplex in the

presence of the agent or drug;

(4) detecting gram-negative bacterial infection in a biological sample comprising:

(a) contacting a sample with a solid surface which is attached to an Invaplex from bacteria suspected of causing the bacterial infection; and

(b) detecting the presence or absence of a complex formed between the Invaplex and antibodies specific therefore in the sample where the presence of a complex formed indicates the presence of the bacterial infection;

(5) detecting gram-negative bacteria infection in a sample comprising:

(a) contacting a sample with a solid surface to which is attached an Invaplex from bacteria suspected of being present in the sample; and

(b) detecting the presence or absence of a complex formed between the Invaplex and the bacteria in the sample where the presence of a complex formed indicates the presence of the bacteria;

(6) an antibody to an Invaplex which recognizes the Invaplex (portion); and

(7) eliciting an antigen-specific immune response in a subject comprising administering to the subject an Invaplex from a gram-negative bacteria along with the antigen where the antigen specific immune response is chosen from a group consisting of cell mediated immune response, humoral immune response and mucosal immune response.

ACTIVITY - Antibacterial.

MECHANISM OF ACTION - Vaccine.

USE - The Invaplex is useful in a composition which is useful as an adjuvant (especially a mucosal adjuvant) for vaccines, biochemical or other substances and as a diagnostic tool, especially for detecting antibody responses which correlates with protection against future infection (e.g. in the form of a bio-sensor).

ADVANTAGE - The Invaplex is an effective adjuvant which results in very little reactogenicity or toxicity in addition to stimulating a potent mucosal and serum immune response when administered along with the antigen. The method for the production of Invaplex produces it in higher yield by minimizing the time to prepare the water extract preparation. The Ipa proteins are extremely labile and degrade rather quickly and the method also uses a volume of water which is 1/20 the volume of the medium used to grow the culture instead of a ratio of 1/10.

Dwg.0/0

TECH UPTX: 20000524

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The gram-negative bacteria is selected from the following: Shigella (especially S. flexneri, S. sonnei, S. boydii, S. dysenteriae), Escherichia (especially E. coli e.g. EIEC), Salmonella, Yersinia, Rickettsia, Brucella, Ehrlichiae, Edwardsiella, Campylobacter, Legionella and **Neisseria**. The invaplex comprises at least one invasin protein e.g. IpaA, IpaB, IpaC, IpaD and LPS. The Invaplex further comprises VirG portions.

Preferred Method: The isolating step is by using an ion exchange matrix. The biological sample is from an animal and the antigen is a viral **antigen**, mammalian cell **surface** molecule, bacterial **antigen**, fungal antigen, protozoan antigen, parasitic antigen and cancer antigens.

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=> fil biosis
FILE 'BIOSIS' ENTERED AT 11:08:20 ON 21 MAR 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 20 March 2002 (20020320/ED)


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     (FILE 'WPIDS' ENTERED AT 11:04:17 ON 21 MAR 2002)
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     FILE 'BIOSIS' ENTERED AT 11:05:11 ON 21 MAR 2002
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L2         25521 S NEISSER? OR MENINGITIDI?
L3         29575 S SURFACE (3A) ANTIGEN#
L4           136 S L2 AND L3
L5           299 S L3 (5A) (DELET? OR MUTAT? OR MODIF? OR TRUNCAT? OR FRAGM?)
L6             0 S L5 AND L2
L7             2 S HIA HOMOLOG?
L8             1 S L7 AND L2
L9             2 S L1 OR L7 OR L8

     FILE 'BIOSIS' ENTERED AT 11:08:20 ON 21 MAR 2002

=> d  all 1-2

L9   ANSWER 1 OF 2  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN   2000:377322  BIOSIS
DN   PREV200000377322
TI   Identification and characterisation of a novel conserved outer membrane
     protein from Neisseria meningitidis.
AU   Peak, Ian R. A.; Srikhanta, Yogitha; Dieckelmann, Manuela; Moxon, E.
     Richard; Jennings, Michael P. (1)
CS   (1) Department of Microbiology and Parasitology, University of Queensland,
     Brisbane, QLD, 4072 Australia
SO   FEMS Immunology and Medical Microbiology, (August, 2000) Vol. 28, No. 4,
     pp. 329-334. print.
     ISSN: 0928-8244.
DT   Article
LA   English
SL   English
AB   We have identified a homologue of the adhesin AIDA-I of Escherichia coli
     in Neisseria meningitidis. This gene was designated
     nhhA (Neisseria hia homologue), as
     analysis of the complete coding sequence revealed that it is more closely
     related to the adhesins Hia and Hsf of Haemophilus influenzae. The
     sequence of nhhA was determined from 10 strains, and found to be
     highly conserved. Studies of the localisation by Western immunoblot
     analysis of total cell proteins and outer membrane complex preparations
     and by immunogold electron microscopy revealed that NhhA is
     located in the outer membrane. A strain survey showed that nhhA
     is present in 85/85 strains of N. meningitidis representative of
     all the major disease-associated serogroups, based on Southern blot
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analysis. It is expressed in the majority of strains tested by Western immunoblot.

CC Physiology and Biochemistry of Bacteria *31000
Genetics and Cytogenetics - General *03502
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Membrane Phenomena *10508
Morphology and Cytology of Bacteria *30500
Genetics of Bacteria and Viruses *31500
Immunology and Immunochemistry - General; Methods *34502

BC **Neisseriaceae** 06507
Enterobacteriaceae 06702

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Immune System (Chemical Coordination and Homeostasis); Infection

IT Chemicals & Biochemicals
outer membrane protein: expression; **Neisseria nhhA** gene (**Neisseriaceae**): expression

IT Methods & Equipment
Western immunoblotting: detection method; immunogold electron microscopy: imaging method

ORGN Super Taxa
Enterobacteriaceae: Facultatively Anaerobic Gram-Negative Rods, Eubacteria, Bacteria, Microorganisms; **Neisseriaceae**: Gram-Negative Aerobic Rods and Cocci, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name
Escherichia coli (Enterobacteriaceae): pathogen; **Neisseria meningitidis** (**Neisseriaceae**): pathogen

ORGN Organism Superterms
Bacteria; Eubacteria; Microorganisms

L9 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:242592 BIOSIS
DN PREV199698790721
TI Identification of a second family of high-molecular-weight adhesion proteins expressed by non-typable Haemophilus influenzae.
AU Barenkamp, Stephen J. (1); St Geme, Joseph W., III
CS (1) Dep. Pediatrics, St. Louis Univ. Sch. Med., Pediatric Res. Inst., Cardinal Glennon Children's Hospital, 1465 South Grand Boulevard, St. Louis, MO 63104 USA
SO Molecular Microbiology, (1996) Vol. 19, No. 6, pp. 1215-1223.
ISSN: 0950-382X.
DT Article
LA English
AB We previously reported that two surface-exposed high-molecular-weight proteins, HMW1 and HMW2, expressed by a prototypic strain of non-typable Haemophilus influenzae (NTHI), mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to 70-75% of NTHI strains. NTHI strains that lack HMW1/HMW2-like proteins remain capable of efficient attachment to cultured human epithelial cells, suggesting the existence of additional adhesion molecules. We reasoned that characterization of high-molecular-weight immunogenic proteins from an HMW1/HMW2-deficient strain might identify additional adhesion proteins. A genomic library was prepared in lambda-EMBL3 with chromosomal DNA from non-typable Haemophilus strain 11, a strain that lacks HMW1/HMW2-like proteins. The library was screened immunologically with convalescent serum from a child naturally infected with strain 11, and phage clones expressing high-molecular-weight recombinant proteins were identified by Western blot analysis. One clone

was identified that expressed a protein with an apparent molecular mass greater than 200 kDa. Transformation of non-adherent Escherichia coli strain DH5-alpha with plasmids containing the genetic locus encoding this protein gave rise to E. coli transformants that adhered avidly to Chang conjunctival cells. Subcloning and mutagenesis studies localized the DNA conferring the adherence phenotype to a 4.8 kbp fragment, and nucleotide sequence analysis further localized the gene encoding the adhesion protein to a 3.3 kbp open reading frame predicted to encode a protein of 114 kDa. The gene was designated hia for Haemophilus influenzae adhesin. Southern analysis revealed an **hia homologue** in 13 of 15 HMW1/HMW2-deficient non-typable H. influenzae strains. In contrast, the hia gene was not present in any of 23 non-typable H. influenzae strains which expressed HMW1/HMW2-like proteins. Identification of this second family of high-molecular-weight adhesion proteins suggests the possibility of developing vaccines based upon a combination of HMW1/HMW2-like proteins and Hia-like proteins which would be protective against disease caused by most or all non-typable H. influenzae.

CC Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Replication, Transcription, Translation *10300
Biophysics - Molecular Properties and Macromolecules *10506
Physiology and Biochemistry of Bacteria *31000
Genetics of Bacteria and Viruses *31500

BC Pasteurellaceae *06703

IT Major Concepts
Biochemistry and Molecular Biophysics; Genetics; Molecular Genetics (Biochemistry and Molecular Biophysics); Physiology

IT Chemicals & Biochemicals
GENBANK-U38617

IT Sequence Data
molecular sequence data; nucleotide sequence; GENBANK-U38617

IT Miscellaneous Descriptors
CHROMOSOMAL DNA

ORGN Super Taxa
Pasteurellaceae: Eubacteria, Bacteria

ORGN Organism Name
Haemophilus influenzae (Pasteurellaceae)

ORGN Organism Superterms
bacteria; eubacteria; microorganisms

RN 175000-29-0 (GENBANK-U38617)

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=> fil medline embase
FILE 'MEDLINE' ENTERED AT 11:10:21 ON 21 MAR 2002

FILE 'EMBASE' ENTERED AT 11:10:21 ON 21 MAR 2002
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     (FILE 'BIOSIS' ENTERED AT 11:08:20 ON 21 MAR 2002)
               DEL HIS Y

     FILE 'MEDLINE, EMBASE' ENTERED AT 11:08:44 ON 21 MAR 2002
L1         28682 S NEISSER?
L2             4 S NHHA OR NHH A OR NH HA OR N HHA
L3             2 S L1 AND L2
L4         73547 S SURFACE (4A) ANTIGEN?
L5           592 S L4 (5A) (DELET? OR MUTAT? OR MODIF? OR TRUNCAT? OR FRAGM?)
L6             4 S L5 AND L1
L7             6 S L3 OR L6
L8             3 DUP REM L7 (3 DUPLICATES REMOVED)

     FILE 'MEDLINE, EMBASE' ENTERED AT 11:10:21 ON 21 MAR 2002

=> d all 1-3

L8   ANSWER 1 OF 3    MEDLINE                              DUPLICATE 1
AN   2000425203     MEDLINE
DN   20351333   PubMed ID: 10891657
TI   Identification and characterisation of a novel conserved outer membrane
     protein from Neisseria meningitidis.
AU   Peak I R; Srikhanta Y; Dieckelmann M; Moxon E R; Jennings M P
CS   Department of Microbiology and Parasitology, The University of Queensland,
     Brisbane, Australia.
SO   FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, (2000 Aug) 28 (4) 329-34.
     Journal code: BP1; 9315554. ISSN: 0928-8244.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200009
ED   Entered STN: 20000922
     Last Updated on STN: 20000922
     Entered Medline: 20000914
AB   We have identified a homologue of the adhesin AIDA-I of Escherichia coli
     in Neisseria meningitidis. This gene was designated nhhA
     (Neisseria hia homologue), as analysis of the complete coding
     sequence revealed that it is more closely related to the adhesins Hia and
     Hsf of Haemophilus influenzae. The sequence of nhhA was
     determined from 10 strains, and found to be highly conserved. Studies of
     the localisation by Western immunoblot analysis of total cell proteins and
     outer membrane complex preparations and by immunogold electron microscopy
     revealed that NhhA is located in the outer membrane. A strain
     survey showed that nhhA is present in 85/85 strains of N.
     meningitidis representative of all the major disease-associated
     serogroups, based on Southern blot analysis. It is expressed in the
     majority of strains tested by Western immunoblot.
CT   Check Tags: Support, Non-U.S. Gov't
      Adhesins, Bacterial: CH, chemistry
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Adhesins, Bacterial: GE, genetics
Adhesins, Bacterial: ME, metabolism
Adhesins, Escherichia coli: GE, genetics
Bacterial Outer Membrane Proteins: CH, chemistry
*Bacterial Outer Membrane Proteins: GE, genetics
*Bacterial Outer Membrane Proteins: ME, metabolism
Conserved Sequence
Escherichia coli: GE, genetics
Escherichia coli: ME, metabolism
Immunohistochemistry
Neisseria meningitidis: GE, genetics
***Neisseria meningitidis: ME, metabolism**
Sequence Homology, Amino Acid
Variation (Genetics)
CN 0 (AIDA-I protein); 0 (Adhesins, Bacterial); 0 (Adhesins, Escherichia coli); 0 (Bacterial Outer Membrane Proteins); 0 (Hsf protein)

L8 ANSWER 2 OF 3 MEDLINE DUPLICATE 2
AN 90131879 MEDLINE
DN 90131879 PubMed ID: 1688906
TI Localization of and immune response to the lipid-modified azurin of the pathogenic **Neisseria**.
AU Trees D L; Spinola S M
CS Department of Microbiology and Immunology, School of Medicine, University of North Carolina, Chapel Hill.
NC AI-07001 (NIAID)
AI-07531 (NIAID)
SO JOURNAL OF INFECTIOUS DISEASES, (1990 Feb) 161 (2) 336-9.
Journal code: IH3; 0413675. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199003
ED Entered STN: 19900328
Last Updated on STN: 19960129
Entered Medline: 19900309
AB The development of vaccines to prevent **Neisseria** infections has been impeded by **antigenic** diversity of most **Neisseria** **surface** components. The lipid-**modified** azurin (Laz), one of two distinct surface proteins recognized by the H.8 monoclonal antibody, is present in all pathogenic **Neisseria**. The mature protein has two domains; one contains an H.8 epitope and the other has extensive homology to azurins, a class of bacterial copper-binding proteins. The cellular location of Laz and the serum immune response to Lax were examined in patients with disseminated **Neisseria** infections. The data demonstrated that Laz is probably contained in the **Neisseria** outer membrane, although unlike most outer membrane proteins it is Sarkosyl soluble. By probing recombinant bacteriophages encoding the H.8 and azurin domains of Laz, results showed that whereas the H.8 epitope is immunogenic in patients with disseminated **Neisseria** infections, the azurin domain of Laz plays little role in eliciting an antibody response in these patients.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
*Antibodies, Bacterial: BI, biosynthesis
Antibodies, Monoclonal: IM, immunology
Antigens, Bacterial: AN, analysis
Antigens, Bacterial: IM, immunology
*Azurin: AN, analysis
Azurin: IM, immunology

*Bacterial Proteins: AN, analysis
Bacteriophages: GE, genetics
Blotting, Western
Cell Membrane: IM, immunology
Epitopes: IM, immunology
Gonorrhea: IM, immunology
Meningococcal Infections: IM, immunology
***Neisseria gonorrhoeae: IM, immunology**
Neisseria gonorrhoeae: UL, ultrastructure
***Neisseria meningitidis: IM, immunology**
Neisseria meningitidis: UL, ultrastructure
RN 12284-43-4 (Azurin)
CN 0 (Antibodies, Bacterial); 0 (Antibodies, Monoclonal); 0 (Antigens, Bacterial); 0 (Bacterial Proteins); 0 (Epitopes)

L8 ANSWER 3 OF 3 MEDLINE DUPLICATE 3
AN 87056087 MEDLINE
DN 87056087 PubMed ID: 3096894
TI **Surface**-exposed **antigenic** cleavage **fragments** of **Neisseria** gonorrhoeae proteins 1A and IB.
AU Schmitt S; Layh G; Buchanan T B
SO INFECTION AND IMMUNITY, (1986 Dec) 54 (3) 841-5.
Journal code: GO7; 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198612
ED Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19861230
AB Whole bacteria, isolated outer membranes, and purified protein I (PI) from one transparent (O-) and two different opaque (O+) phenotype gonococcal strains (serogroups I, II, and III; PI serotypes 1, 5, and 9b) were each treated with tolylsulfonyl phenylalanyl chloromethyl ketone-trypsin, alpha-chymotrypsin, and proteinase K. Protein IA (PIA) of strain 7122 (O-, serotype 1, serogroup I) was resistant to proteolysis by tolysulfonyl phenylalanyl chloromethyl ketone-trypsin and alpha-chymotrypsin and only slightly affected by proteinase K, as long as it was associated with intact bacteria or isolated outer membranes. Purified PIA however was cleaved by these enzymes, resulting in two to five fragments. In contrast, all preparations of strains 5766 opaque phenotype (O+, serotype 7, serogroup II) and 1955 (O+, serotype 9b, serogroup III) were accessible to proteolysis, resulting in cleavage fragments of PIB compatible to those described previously by O. Barrera and J. Swanson (Infect. Immun. 44:565-568, 1984), M. S. Blake et al. (Infect. Immun. 33:212-222, 1981), and Blake (in G. K. Schoolnik, ed., The Pathogenic **Neisseriae**, 1985). Our data indicated that the purified PIB fraction was more accessible to proteases than the PIBs of whole bacteria or outer membranes. The fragmentation pattern of PIA cleavage products were quite different from PIB fragments, consistent with the different structure of these two groups of PI molecules. Time-dependent cleavage experiments with proteases, i.e., alpha-chymotrypsin, indicated that PIA was subsequently cleaved into smaller fragments. Highly reactive monoclonal antibodies, each specific for a surface-exposed epitope of PIA of strain 7122 or PIB of strains 5766 and 1955, as assessed by coagglutination, Western blot, and immunofluorescence, were reacted with PIA and PIB cleavage fragments in Western blot experiments. All cleavage fragments of the purified PIA and PIB preparations with molecular weights of greater than or equal to 14,200 showed immune reaction in Western blotting, whereas whole cell and

outer membrane PIB fragments were less reactive with the specific monoclonal antibodies.

CT Check Tags: Support, Non-U.S. Gov't
Antibodies, Monoclonal: IM, immunology
*Antigens, Bacterial: IM, immunology
Antigens, Bacterial: IP, isolation & purification
Antigens, Surface: IM, immunology
*Bacterial Outer Membrane Proteins: IM, immunology
Bacterial Outer Membrane Proteins: IP, isolation & purification
Immunosorbent Techniques
Molecular Weight
***Neisseria gonorrhoeae: IM, immunology**
Peptide Fragments: IM, immunology
Peptide Hydrolases: ME, metabolism
Species Specificity

CN 0 (Antibodies, Monoclonal); 0 (Antigens, Bacterial); 0 (Antigens, Surface); 0 (Bacterial Outer Membrane Proteins); 0 (Peptide Fragments); EC 3.4 (Peptide Hydrolases)